Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 04-15-2011

Submission # 5

The following request has been:

- ○ Approved
- ☒ Denied

Gennrich, Jane - Medicaid

From: Paul J Setlak [paul.setlak@abbott.com]
Sent: Monday, March 14, 2011 5:38 PM
To: Gennrich, Jane - Medicaid; Eide, Tamara J. - Medicaid
Subject: Idaho Medicaid P&T Committee Request - AndroGel
Attachments: Basaria et al, 2010.pdf

March 14, 2011

Pharmacy & Therapeutics Committee
Attention: Tami Eide, Pharm.D.
3232 Elder Street
Boise, Idaho 83705

Dear Dr. Eide:

Thank you for your unsolicited request for updated clinical information on AndroGel®. Please find enclosed updated clinical information for the product being reviewed, per your direction found on the website (http://healthandwelfare.idaho.gov/Medical/PrescriptionDrugs/PTCommittee/tabid/207/Default.aspx), for consideration as part of the upcoming State of Idaho P&T Committee Drug Review Meeting to be held April 15, 2011.

AndroGel®

1. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010 Jul 8;363(2):109-22.

For full prescribing information, please see the most up to date package insert located at:
AndroGel®: http://rxabbott.com/pdf/androgel_PI.pdf
Additionally, based on the State of daho promulgated rules regarding "(3) new studies released since the last review," please permit this correspondence to also serve as a request to provide oral presentation based on the clinical updates provided.

Please understand that this information is intended to provide only a clinical update of AndroGel®. If you would like additional information or have more questions please contact me at 773-320-7057.

Thank you and have a wonderful day.

Sincerely,
Dr. Paul Setlak

Paul J Setlak, Pharm.D.
Regional Clinical Executive
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Adverse Events Associated with Testosterone Administration

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ABSTRACT

BACKGROUND

Testosterone supplementation has been shown to increase muscle mass and strength in healthy older men. The safety and efficacy of testosterone treatment in older men who have limitations in mobility have not been studied.

METHODS

Community-dwelling men, 65 years of age or older, with limitations in mobility and a total serum testosterone level of 100 to 350 ng per deciliter (3.5 to 12.1 nmol per liter) or a free serum testosterone level of less than 50 pg per milliliter (173 pmol per liter) were randomly assigned to receive placebo gel or testosterone gel, to be applied daily for 6 months. Adverse events were categorized with the use of the Medical Dictionary for Regulatory Activities classification. The data and safety monitoring board recommended that the trial be discontinued early because there was a significantly higher rate of adverse cardiovascular events in the testosterone group than in the placebo group.

RESULTS

A total of 209 men (mean age, 74 years) were enrolled at the time the trial was terminated. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the participants. During the course of the study, the testosterone group had higher rates of cardiac, respiratory, and dermatologic events than did the placebo group. A total of 23 subjects in the testosterone group, as compared with 5 in the placebo group, had cardiovascular-related adverse events. The relative risk of a cardiovascular-related adverse event remained constant throughout the 6-month treatment period. As compared with the placebo group, the testosterone group had significantly greater improvements in leg-press and chest-press strength and in stair climbing while carrying a load.

CONCLUSIONS

In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy. (ClinicalTrials.gov number, NCT00240981.)

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LIMITED MOBILITY IS A COMMON GERIATRIC condition that is a predictor of disability, poor quality of life, and death.[1-7] In men, an age-related decline in the serum testosterone concentration is associated with reduced muscle mass and lower-extremity strength, limitations in physical function, and poor mobility.[8-13] Testosterone supplementation increases muscle mass and strength and leg power, all of which are important determinants of mobility.[14-21] Previous trials of testosterone supplementation have been conducted primarily among healthy older men. The safety and efficacy of testosterone treatment in improving muscle performance and physical function in older men with limitations in mobility have not been studied.

The Testosterone in Older Men with Mobility Limitations (TOM) trial was a placebo-controlled, randomized trial that was designed to determine the effects of testosterone administration on lower-extremity strength and physical function in older men with limitations in mobility and low serum levels of total or free testosterone.[22] In December 2009, a data and safety monitoring board, established by the National Institute on Aging, determined that the incidence of adverse cardiovascular events in the TOM trial was significantly higher in the testosterone group than in the placebo group. The members of the data and safety monitoring board therefore recommended that enrollment and administration of the study medications be discontinued. We report here the adverse events associated with testosterone therapy in the TOM trial. The effects of testosterone therapy on efficacy outcomes are reported briefly.

METHODS

STUDY DESIGN

The TOM trial was a parallel-group, randomized, placebo-controlled, double-blind trial involving community-dwelling men. The trial was conducted at three recruitment sites: Boston University Medical Center, New England Research Institutes, and the Veterans Affairs Boston Healthcare System. The trial protocol and amendments, as well as the statistical analysis plan, are available with the full text of this article at NEJM.org.

The trial was funded primarily by the National Institute on Aging of the National Institutes of Health under a cooperative agreement. Additional support was provided by the resources of the Boston Claude D. Pepper Older Americans Independence Center and the Boston University Clinical and Translational Science Institute. Testosterone and placebo gels for the study were provided by Auxilium Pharmaceuticals, which had no role in the design or implementation of the study, the analysis or interpretation of the data, or the preparation of the manuscript.

The trial was designed by the authors, and the trial protocol was approved by the institutional review board at each participating center. The design and maintenance of the database and the data collection were supervised by the Boston University School of Public Health Data Coordinating Center. The manuscript was written by the authors, and the decision to submit the manuscript for publication was made jointly by the authors and the trial's data and safety monitoring board (see the Appendix). The authors vouch for the accuracy and completeness of the data and all analyses.

STUDY PARTICIPANTS

The study participants were men, 65 years of age or older, who had a total serum testosterone level between 100 and 350 ng per deciliter (3.5 to 12.1 nmol per liter) or a free serum testosterone level of less than 50 pg per milliliter (173 pmol per liter), as measured in a blood sample obtained in the morning. Participants were also required to have evidence of limitations in mobility, defined as having difficulty walking two blocks on a level surface or climbing 10 steps and having a score between 4 and 9 on the Short Physical Performance Battery (which measures performance on a scale of 0 to 12, with higher scores indicating better performance).[22] Exclusion criteria were uncontrolled hypertension, unstable angina, myocardial infarction within 3 months before enrollment, New York Heart Association class III or class IV congestive heart failure, prostate or other active cancer, severe lower urinary tract symptoms, untreated severe obstructive sleep apnea, glucocorticoid or anabolic steroid therapy, a glycated hemoglobin level higher than 8.5%, a hematocrit higher than 48%, a prostate-specific antigen level higher than 4 ng per milliliter, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 40. Further details of the trial inclusion and exclusion

criteria are provided in Section A in the Supplementary Appendix, available at NEJM.org. All participants provided written informed consent.

PROCEDURES

Participants were stratified according to age (65 to 75 years or older than 75 years) and were randomly assigned to receive 10 g of a transdermal gel containing either placebo or 100 mg of testosterone (Testim 1%,[23] Auxilium Pharmaceuticals), to be applied once daily for 6 months. Two weeks after randomization was performed, the dose was adjusted if the average of two testosterone measurements was less than 500 ng per deciliter (17.4 nmol per liter), in which case the dose was increased to 15 g daily, or more than 1000 ng per deciliter (34.7 nmol per liter), in which case the dose was decreased to 5 g daily.

The primary efficacy outcome was the change from baseline in maximal voluntary muscle strength in a leg-press exercise.[24] Secondary efficacy outcomes included changes from baseline in chest-press strength, 50-m walking speed, stair-climbing speed and power, and a lift-and-lower test.[24] Measurements were performed at baseline and at week 24, or at the last visit in the case of participants who discontinued the study medication before 6 months. Testosterone was measured with the use of an immunoassay[25] (Quest) with a sensitivity of 10 ng per deciliter (0.35 nmol per liter), and sex hormone–binding globulin was measured with the use of an immunofluorometric assay[15] (Delfia, Wallac [now PerkinElmer]) with a sensitivity of 2.5 nmol per liter; free testosterone was calculated.[26] Further details of the trial procedures are provided in Section A in the Supplementary Appendix.

SAFETY MONITORING

Safety monitoring included measurements of hemoglobin, hematocrit, prostate-specific antigen, and serum chemical levels; a prostate examination; an assessment of urinary tract symptoms; and an assessment of adverse events. Adverse events were categorized by personnel at KAI Research (Rockville, MD), a contract research organization, according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class categorization. The data and safety monitoring board reviewed serious adverse events as they occurred and cumulative adverse events every 6 months.

An imbalance in a broad array of adverse cardiac events between the two study groups prompted the data and safety monitoring board to review unblinded data in December 2009 and to request analyses of two categories of adverse events in addition to the MedDRA-classified cardiac events. The first, "cardiovascular-related events," included MedDRA-classified cardiac events as well as events that the data and safety monitoring board considered to be cardiovascular in nature but that were included in other MedDRA System Organ Class categories: stenting and bypass procedures (included in the MedDRA category of surgical and medical procedures), peripheral edema (included in the category of general disorders), elevated blood pressure, arrhythmias, and electrocardiographic changes (included in the investigations category), and stroke and syncope (included in the category of nervous system disorders). The second analysis included "atherosclerosis-related events," such as myocardial infarction, sudden death, angioplasty, coronary-artery bypass surgery, and stroke. Further details of the safety monitoring procedures are provided in Section A in the Supplementary Appendix.

STATISTICAL ANALYSIS

We had planned to enroll 252 men in the trial, since we had estimated that with this sample size, the study would have 90% power to show an increase of 245 newtons (N) (25 kg) in bilateral leg-press strength with testosterone therapy, with a standard deviation for the treatment effect of 540 N (55 kg), on the basis of previous studies,[27] assuming a 20% loss to follow-up and a probability of type I error of 0.05. At the time the analyses of adverse events were performed (December 15, 2009), a total of 209 men had been randomly assigned to a trial group.

The primary analysis reported here was a between-group comparison of the incidence of adverse events among the 209 participants who had been randomly assigned before the termination of the trial. The proportion of subjects in each group with one or more adverse events was calculated for each MedDRA System Organ Class, and these proportions were compared with the use of chi-square tests and Fisher's exact tests. Estimated odds ratios for events, both unadjusted and adjusted for baseline risk factors, and associated 95% confidence intervals were calculated with the

use of logistic regression. The time to the report of the first adverse event or to data censoring was determined for cardiovascular-related events, dermatologic events, and events that necessitated referral for medical evaluation and was compared between the two trial groups with the use of the Kaplan–Meier method and Cox proportional-hazards models. Post hoc sensitivity analyses were performed in which subjects who had specific risk factors at baseline that might have affected the outcomes were excluded. We also performed a limited efficacy analysis for this report, comparing mean changes in efficacy outcomes with the use of two-sample Student's t-tests. Further details of the statistical methods are provided in Section A in the Supplementary Appendix.

RESULTS

ENROLLMENT OF SUBJECTS AND DISCONTINUATION OF THE STUDY

Enrollment in the trial took place between September 2005 and December 2009. On December 31, 2009, the data and safety monitoring board recommended that the study intervention and enrollment be discontinued, owing to a higher pro-

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Testosterone Gel (N=106)	Placebo Gel (N=103)	P Value†
Enrollment site — no. (%)			0.72
Boston University Medical Center	26 (25)	30 (29)	
New England Research Institutes	70 (66)	65 (63)	
Veterans Affairs Boston Healthcare System	10 (9)	8 (8)	
Age — yr	74±6	74±5	0.84
Body-mass index‡	29.7±4.1	30.0±4.2	0.58
Race — no./total no. (%)§			0.04
Black	15/105 (14)	4/102 (4)	
White	87/105 (83)	93/102 (91)	
Asian or Pacific Islander	1/105 (1)	1/102 (1)	
Other¶	2/105 (2)	4/102 (4)	
Hispanic or Latino ethnic group — no./total no. (%)§	2/97 (2)	2/88 (2)	0.99
Testosterone level‖			
Total — ng/dl	250±57	236±66	0.11
Free — pg/ml	48±12	43±14	0.003
Score on the Short Physical Performance Battery**	7.6±1.5	7.7±1.4	0.74
Measure of strength			
Leg press			0.51
No. who performed the test	75	69	
Force — newtons	1947±430	1991±365	
Chest press			0.74
No. who performed the test	66	62	
Force — newtons	424±112	418±102	
Dominant-hand grip			0.46
No. who performed the test	97	92	
Force — kg	27.3±6.7	26.6±7.4	
50-m walking test			
Without a load			0.64
No. who performed the test	84	79	
Speed — m/sec	1.62±0.40	1.60±0.37	
With a load			0.99
No. who performed the test	54	49	
Speed — m/sec	1.63±0.34	1.63±0.36	

Table 1. (Continued.)

Characteristic	Testosterone Gel (N=106)	Placebo Gel (N=103)	P Value†
Stair-climbing test			
Without a load			0.59
No. who performed the test	72	68	
Power — W	329±113	320±90	
With a load			0.44
No. who performed the test	69	66	
Power — W	363±135	346±115	
Lift-and-lower test††			0.77
No. who performed the test	64	58	
Score	24.4±9.2	23.9±9.8	

* Plus–minus values are means ±SD.
† The P values were calculated with the use of Fisher's exact test and Student's t-test.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race or ethnic group was determined by self-report.
¶ Included in this category were subjects who described themselves as being of mixed race, who did not report their race, or who described themselves in categories that were not black, white, or Asian–Pacific Islander.
‖ To convert the values for total testosterone to nanomoles per liter, multiply by 0.0347. To convert the values for free testosterone to picomoles per liter, multiply by 3.467. Total and free testosterone levels were measured in a single blood sample that was obtained between 7 a.m. and 11 a.m. The subjects were eligible if they had a total testosterone level between 100 and 350 ng per deciliter or a free testosterone level of less than 50 pg per milliliter.
** Scores on the Short Physical Performance Battery range from 0 to 12, with higher scores indicating better performance.
†† The scores on the lift-and-lower test refer to the number of shelves a subject was able to touch with a weighted basket in 1 minute. Higher scores indicate better performance.

portion of adverse events in the testosterone group than in the placebo group. Of the target sample of 252 men, 209 had been randomly assigned at the time the analyses of adverse events were performed (December 15, 2009), and were included in the safety analyses (Fig. 1 in the Supplementary Appendix). Of the 209 randomly assigned men, 129 had completed the 6-month intervention period, and an additional 47 had received the study medication for 12 or more weeks and had undergone at least one outcome assessment after randomization. The 176 men with a baseline assessment and at least one outcome assessment were included in the efficacy analyses.

BASELINE CHARACTERISTICS OF THE MEN

The mean age of the men was 74 years. The mean level of total testosterone was 243 ng per deciliter (8.4 nmol per liter), and the mean level of free testosterone was 46 pg per milliliter (160 pmol per liter). The men had substantial limitations in mobility, as indicated by a mean score on the Short Physical Performance Battery of 7.6 and a mean 4-m walking speed of 0.94 m per second (Table 1). Both study groups had a high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and known cardiovascular disease (Table 2). A greater proportion of men in the testosterone group than in the placebo group reported that they had received a diagnosis of hyperlipidemia or were taking a statin.

TESTOSTERONE DOSE AND ADHERENCE

After adjustment of the testosterone dose to achieve the target range, 29 men in the testosterone group received 5 g of the testosterone gel daily, 61 received 10 g, and 16 received 15 g. Adherence, as assessed by a count of the unused gel tubes, was greater than 90% in both groups.

LABORATORY AND PHYSIOLOGICAL DATA

The mean (±SD) testosterone levels were 574±403 ng per deciliter (19.9±14.0 nmol per liter) in the testosterone group (after adjustment of the dose to achieve the target range) and 292±160 ng per deciliter (10.1±5.6 nmol per liter) in the placebo group. In the testosterone group, as compared with the placebo group, there was a significant increase in hemoglobin and hematocrit levels and a signifi-

Table 2. Baseline Characteristics Related to Cardiovascular Risk.*

Characteristic	Testosterone (N=106)	Placebo (N=103)	P Value†
Preexisting cardiovascular disease — no. (%)‡	56 (53)	48 (47)	0.41
Obesity — no. (%)§	48 (45)	50 (49)	0.68
Blood pressure — mm Hg			
Systolic	137±15	137±14	0.98
Diastolic	77±10	75±10	0.21
Hypertension — no. (%)¶	90 (85)	80 (78)	0.21
Antihypertensive therapy — no. (%)	90 (85)	75 (73)	0.04
Diabetes mellitus — no. (%)¶	25 (24)	28 (27)	0.63
Glycated hemoglobin — %	6.2±0.7	6.1±0.7	0.32
Lipids — mg/dl‖			
Cholesterol			
Total	165±35	171±39	0.24
LDL	89±30	92±33	0.51
HDL	46±13	48±18	0.20
Triglycerides	159±111	143±69	0.20
Hyperlipidemia — no. (%)¶	67 (63)	51 (50)	0.05
Statin therapy — no. (%)	66 (62)	48 (47)	0.03
Framingham Risk Score — %**	22±6	21±6	0.31
Smoking status — no./total no. (%)			0.66
Never smoked	27/104 (26)	21/103 (20)	
Former smoker	68/104 (65)	73/103 (71)	
Current smoker	9/104 (9)	9/103 (9)	

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† The P values were calculated with the use of Fisher's exact test and Student's t-test.
‡ Preexisting cardiovascular disease was defined as self-reported coronary artery disease, cerebrovascular disease, peripheral vascular disease, aortic aneurysm, congestive heart failure, or arrhythmia.
§ Obesity is defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more.
¶ Hypertension, diabetes, and hyperlipidemia were considered to be present if the participant reported having received the diagnosis or if he was receiving medication for the condition.
‖ In the testosterone group, data on total and HDL cholesterol and triglyceride levels were available for 105 men, and data on LDL cholesterol level for 103 men; in the placebo group, data on HDL and LDL cholesterol and triglyceride levels were available for 101 men, and data on total cholesterol level for 102 men.
** Data on the Framingham Risk Score were available for 103 men in the testosterone group and 101 men in the placebo group.

cant decrease in high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels (Table 1 in the Supplementary Appendix). Changes in blood pressure did not differ significantly between the testosterone and placebo groups (change in systolic pressure, −2.9±12.9 mm Hg vs. −4.6±14.8 mm Hg; change in diastolic pressure, −1.3±7.1 mm Hg vs. −1.3±7.8 mm Hg).

ADVERSE EVENTS

In the testosterone group, as compared with the placebo group, there were significantly more adverse events and significantly more subjects who reported one or more adverse events (Table 2 in the Supplementary Appendix). Twice as many men in the testosterone group as in the placebo group were referred for medical evaluation owing to an adverse event. Men who were assigned to testosterone also reported a greater number of serious adverse events and a greater number of adverse events that were considered to be life-threatening, although the differences between the groups were not significant (Table 3 in the Supplementary Appendix).

Significantly more men in the testosterone group than in the placebo group had adverse events in three MedDRA categories: cardiac disorders; respiratory, thoracic, and mediastinal disorders; and skin and subcutaneous tissue disorders (Table 2 in the Supplementary Appendix). Of particular concern to the data and safety monitoring board was the greater number of subjects with adverse cardiac events in the testosterone group than in the placebo group (10 vs. 1) (Table 3). In accordance with the recommendation of the data and safety monitoring board, two additional analyses of cardiovascular events were performed (Table 3). A total of 23 men in the testosterone group and 5 in the placebo group had cardiovascular-related events; 7 men in the testosterone group and 1 in the placebo group had atherosclerosis-related events.

The risk of a cardiovascular-related adverse event remained significantly greater among men in the testosterone group than among men in the placebo group after adjustment for age group, body-mass index, smoking status, high-density lipoprotein cholesterol level, and presence or absence of diabetes, hyperlipidemia, and hypertension (Table 4). In time-to-event analyses, the relative risk of a cardiovascular-related event remained constant throughout the 24-week intervention period (Fig. 1). There were few adverse events during the 3-month observation phase after the end of the intervention period.

There was no evidence of a significant relationship between potential risk factors and cardiovascular-related events in time-to-event analyses (Fig. 2 in the Supplementary Appendix). Men with testosterone levels in the highest quartile during the intervention period, as compared with all other subjects, were at elevated risk for cardiovascular-related events (hazard ratio, 2.4; $P=0.05$). Among subjects who were randomly assigned to the testosterone group, testosterone levels during the intervention period were available for 81 subjects. Cardiovascular-related events were reported in 4 of 14 subjects with testosterone levels higher than 1000 ng per deciliter during the treatment period, by 5 of 21 with levels of 500 to 1000 ng per deciliter, and by 7 of 46 subjects with levels of less than 500 ng per deciliter.

One man in the testosterone group had a hematocrit that was higher than 54%, and one reported having received a diagnosis of prostate cancer. One man in the placebo group underwent transurethral resection of the prostate.

SENSITIVITY ANALYSES

Sensitivity analyses were performed to determine the effect on the results when subjects who had baseline characteristics that might have affected the outcomes were excluded. The results of these sensitivity analyses with respect to the risk of adverse events associated with assignment to the testosterone group were consistent with the results of the analyses of data from the overall population (Section B in the Supplementary Appendix). Adjustment for baseline self-reported mobility status and Short Physical Performance Battery score had no effect on the results.

EFFICACY OUTCOMES

In an analysis involving all the men who underwent at least one outcome assessment after randomization, men who were assigned to testosterone, as compared with those assigned to placebo, had significantly greater increases in leg-press strength, chest-press strength, and stair-climbing power while carrying a load. Changes in gait speed without a load and stair-climbing power without a load did not differ significantly between the groups (Table 5). Adjustment for baseline self-reported mobility status and Short Physical Performance Battery score had no effect on the results.

DISCUSSION

In this study of older men with low testosterone levels and limitations in mobility, random assignment to daily application of a testosterone gel, as compared with a placebo gel, was associated with a greater frequency of adverse events, particularly cardiovascular, respiratory, and dermatologic events. The divergence between the groups in the incidence of cardiovascular adverse events was maintained over the 6-month intervention period and did not diminish during the 3-month observation phase that followed the intervention period. The increased cardiovascular risk in the testosterone group was seen with all three definitions of cardiovascular events, and the increase persisted after adjustment for baseline risk factors. The increased risk was also evident in sensitivity analyses adjusted for baseline mobility status and Short Physical Performance Battery score and in sensitivity analyses performed after the exclusion of subjects whose eligibility deviated from the planned criteria. The pattern of adverse cardiovascular events associated with testosterone therapy was considered by the data and safe-

ty monitoring board to be of sufficient concern to warrant termination of the trial.

The generalizability of our data about the safety of testosterone therapy is limited by several factors. First, cardiovascular events were not a planned primary or secondary outcome, and therefore, a structured evaluation of cardiovascular events was not performed, a factor that may have influenced the ascertainment of events. Most of the cardiovascular-related events were verified from medical records or by direct examination. Second, the sample, although larger than those in

Table 3. Subjects with One or More Cardiovascular-Related Adverse Events.*

Subject No.	Adverse Event	MedDRA-Classified Cardiac Event	Cardiovascular-Related Event	Atherosclerosis-Related Event	Method of Confirmation†
			no. of events		
Testosterone group					
1	Acute coronary syndrome and chest pain	1	2	1	Review of medical records
2	Chest pain		1	1	Examination by study physician
3	Syncope		1		Self-report
4	Syncope		1		Self-report
5	Myocardial infarction treated with angioplasty and placement of pacemaker	1	1	1	Review of medical records
6	Myocardial infarction	1	1	1	Review of medical records
7	Angioplasty and coronary-artery bypass grafting		1	1	Review of medical records
8	Peripheral edema		1		Examination by study physician
9	Peripheral edema		1		Examination by study physician
10	Ectopy on ECG (premature ventricular contractions, couplets)	1	1		ECG evaluation by study physician
11	Left ventricular strain pattern during exercise testing	1	1		ECG evaluation by study physician
12	ST-segment depression during exercise testing		1	1	ECG evaluation by study physician
13	Elevated blood pressure		1		Examination by study physician
14	Atrial fibrillation with rapid ventricular rate and shortness of breath and exacerbation of congestive heart failure, which necessitated hospitalization	2	2		Examination by study physician (atrial fibrillation) and report of primary care physician (exacerbation of congestive heart failure)
15	Stroke		1		Review of medical records
16	Elevated blood pressure and atrial fibrillation	1	1		Review of medical records
17	Peripheral edema		1		Examination by study physician
18	Peripheral edema		1		Examination by study physician
19	Elevated blood pressure		1		Examination by study physician
20	Tachycardia with fatigue	1	1		Self-report
21	Death, suspected myocardial infarction	1	1	1	Notification by physician
22‡	Peripheral edema		1		Examination by study physician
23	Congestive heart failure exacerbation	1	1		Review of medical records

Table 3. (Continued.)

Subject No.	Adverse Event	MedDRA-Classified Cardiac Event	Cardiovascular-Related Event	Atherosclerosis-Related Event	Method of Confirmation†
			no. of events		
Placebo group					
1	Syncope resulting in hospitalization		1		Self-report
2	Tachycardia		1		Examination by study physician
3	Elevated blood pressure		1		Examination by study physician
4	Arrhythmia–ectopy noted on ECG before exercise testing	1	1		Examination by study physician
5	Carotid bruit and carotid-artery plaque identified on ultrasonography		1	1	Examination by study physician and review of medical records

* In addition to an assessment of cardiac events as categorized with the use of the Medical Dictionary for Regulatory Activities (MedDRA) classification, the data and safety monitoring board requested two analyses. The first included MedDRA-classified cardiac events plus events that the data and safety monitoring board considered to be cardiovascular in nature but that were included in other MedDRA System Organ Class categories: stenting and bypass procedures (included in the MedDRA category of surgical and medical procedures); peripheral edema (included in the category of general disorders); elevated blood pressure, arrhythmias, and electrocardiographic changes (included in the investigations category); and stroke and syncope (included in the category of nervous system disorders). For clarity, these adverse events are listed as cardiovascular-related events. The second analysis included atherosclerosis-related events, which were events that were directly related to atherosclerotic vascular disease, such as myocardial infarction, sudden death, angioplasty, coronary-artery bypass grafting, and stroke. ECG denotes electrocardiogram.

† Medical records were reviewed if an adverse event was reported and records were available to document that event.

‡ Two men, both in the testosterone group, underwent elective vascular procedures during treatment that were not included in these analyses since they were deemed to have been related to preexisting conditions: Subject 22 underwent elective surgery to repair an aortic aneurysm, and another participant, not listed in this table, underwent prescheduled elective angioplasty and placement of a stent in his leg owing to peripheral vascular disease. The results of the analyses did not change when these two events were included.

most previous trials, was small, and the number of adverse events was small. The results of individual small trials may not be confirmed in large trials,[28] and trials that have been stopped early tend to overestimate treatment differences. Third, the clinical characteristics of our study population differ from those of most other populations in which testosterone therapy has been administered in a clinical setting or as part of a clinical trial. Men who were younger than 65 years of age and men with severe hypogonadism were excluded from the trial. Participants had substantial limitations in mobility and a high prevalence of chronic conditions, including preexisting heart disease, obesity, diabetes, and hypertension. Frail elderly men with limitations in mobility are more likely to have clinical and subclinical cardiovascular disease than are those who do not have limitations in mobility.[29,30]

Previous studies provide very limited data to either reinforce or contradict the findings in this study with respect to the effects of testosterone therapy in older men with limited mobility. Meta-analyses of previous trials of testosterone therapy have not shown significant increases in cardiovascular risk with testosterone therapy, although nonsignificant increases have been noted among participants of all ages,[31-33] as well as among older men.[31,33] The trials in these meta-analyses were limited by inadequate methods of ascertaining adverse events or the poor quality of data on adverse events, by the small numbers of events or the small numbers of older participants, or by intervention periods that were shorter than the 6-month intervention in this trial. Some epidemiologic studies have shown that low testosterone levels are an independent risk factor for death from cardiovascular causes and from all causes.[34-37] However, differences between the effects of endogenous hormones and those of pharmacologic hormonal therapy, as well as differences in the duration of exposure to testosterone, could contribute to the apparent discrepancies between these epidemiologic data and the results of our trial.

It is not likely that the adverse cardiovascular

Table 4. Risk of Adverse Events with Testosterone Therapy, According to Category.*

Event Category	Total Risk		Instantaneous Risk	
	Odds Ratio (95% CI)		Hazard Ratio (95% CI)	
	unadjusted	*adjusted*	*unadjusted*	*adjusted*
MedDRA cardiac†	10.6 (1.3–84.5)	NA‡	10.5 (1.3–82.4)	NA‡
Atherosclerosis-related§	7.2 (0.9–59.7)	NA‡	7.1 (0.9–57.8)	NA‡
Cardiovascular-related¶	5.4 (2.0–14.9)	5.8 (2.0–16.8)	5.0 (1.9–13.2)	5.5 (2.0–14.8)
Dermatologic‖	2.6 (1.1–6.2)	4.9 (1.7–14.6)	2.6 (1.1–5.9)	4.8 (1.7–13.0)
Necessitating referral for medical evaluation	2.3 (0.98–5.3)	5.2 (1.8–14.6)	2.3 (1.1–5.2)	5.2 (2.0–13.5)

* Total risk refers to the risk of an adverse event occurring over the entire study period after randomization, which included the 24-week treatment period and the subsequent 12-week observation phase. Instantaneous risk refers to the risk of an adverse event occurring at any specific time. Unadjusted odds ratios and hazard ratios were estimated with the use of simple logistic regression. Adjusted odds ratios and hazard ratios were estimated with the use of multiple logistic regression, with adjustment for age group; body-mass index; presence or absence of diabetes, hypertension, and hyperlipidemia; and high-density lipoprotein cholesterol level. Given the small number of subjects in each cell, the ability to adjust for baseline risk factors is limited, and results should be interpreted conservatively. When 104 men with preexisting self-reported cardiovascular, cerebrovascular, or peripheral vascular disease, with or without congestive heart failure and arrhythmias, were excluded, 9 men treated with testosterone had cardiovascular-related events, as compared with 2 men receiving placebo gel (odds ratio, 5.8; 95% confidence level [CI] 1.2 to 28.4; P=0.03). Three men in the testosterone group had MedDRA cardiac events and two had atherosclerosis-related events, as compared with no men with these events in the placebo group.

† Included are adverse events that were classified as cardiac according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

‡ Adjusted estimates are not applicable (NA) because there was only one event in the placebo group.

§ Included are adverse events that were classified, according to the recommendation of the data and safety monitoring board, as having been directly related to atherosclerotic vascular disease (e.g., myocardial infarction, sudden death, angioplasty, coronary-artery bypass grafting, and stroke).

¶ At the recommendation of the data and safety monitoring board, we included in this analysis, in addition to cardiac events in the MedDRA "Cardiac" category, those that were considered to be cardiovascular in nature but which were included in other MedDRA System Organ Class categories: stenting and bypass procedures (included in the MedDRA "Surgical and Medical Procedures" category); peripheral edema (included in the "General Disorders" category); elevated blood pressure, arrhythmias, and electrocardiographic changes (included in the "Investigations" category); and stroke and syncope (included in the "Nervous System Disorders" category).

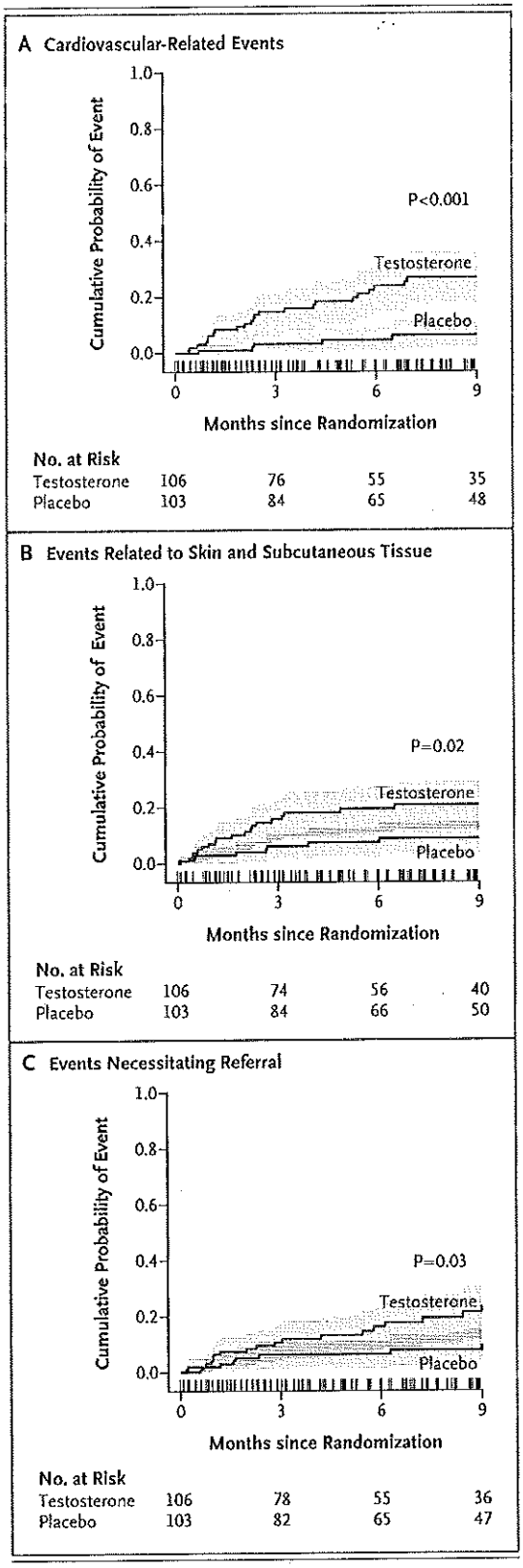
‖ For dermatologic events, unadjusted odds ratios and hazard ratios were estimated with the use of Cox proportional-hazards models. Adjusted odds ratios and hazard ratios were estimated with the use of multivariate proportional-hazards models, with adjustment for age group, body-mass index, presence or absence of diabetes, hypertension, and hyperlipidemia, and high-density lipoprotein cholesterol level.

events seen in the TOM trial are a consequence of an unusual protocol for testosterone administration (Table 4 in the Supplementary Appendix). The upper limit of the testosterone threshold used for inclusion in the trial is not dissimilar to that used in most other trials.[16-19,38-47] The testosterone doses in this trial may have been higher than those that are typically used in clinical practice[48] and were higher than the doses used in some previous trials[17,18,39-42] but were similar to those in other trials.[16,21,43-46] The average testosterone concentrations during the intervention period among men in our testosterone group were in the middle of the normal range for young men; these levels were higher than those in some testosterone trials[17,18,39-42] but did not differ from levels reported in other trials.[16,19,21,43-46]

The cardiovascular adverse events reported in the TOM trial were diverse and may have variable clinical importance. The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone. The results of several separate analyses were consistent with the initial observation of a significant difference, but these analyses were not entirely independent of one another. In interpreting these findings, it is essential to recognize the role that chance may have played in the outcomes we observed.

Figure 1. Time-to-Event Analysis of Adverse Events, According to Body System.

Kaplan–Meier estimates of the cumulative probability of incident cardiovascular-related adverse events (Panel A), events related to skin and subcutaneous tissue (Panel B), and events necessitating referral for medical evaluation (Panel C), from randomization to the end of the planned observation phase (9 months after randomization) are shown for the testosterone and placebo groups. The 95% confidence intervals are indicated by the shaded areas. The notches on the x axis show the distribution of censoring times before 9 months among participants in both groups. The P values were calculated from an unadjusted comparison of curves with the use of the log-rank test.



The diversity of cardiac adverse events also renders the events less susceptible to a single mechanistic explanation. Testosterone causes salt and water retention,[49-51] particularly in older men,[14] and this could contribute to edema, hypertension, and congestive heart failure, although there are some trials in which testosterone has been administered in men with congestive heart failure.[39,40] Testosterone and associated increases in estradiol may promote inflammation, coagulation, and platelet aggregation.[52] The use of anabolic steroids has been associated with left ventricular hypertrophy and systolic and diastolic dysfunction.[53,54] Changes in plasma lipid levels would not account for the rapid divergence in rates of cardiovascular adverse events.

Testosterone therapy was associated with significant improvements in leg-press and chest-press strength and in stair-climbing power with a load. Inferences regarding efficacy are limited because of the attenuation of statistical power owing to the early termination of the trial.

In conclusion, we evaluated the effect of testosterone supplementation in men 65 years of age or older who had limitations in mobility and low serum levels of total or free testosterone. The trial was stopped before enrollment had been completed because of an incidence of adverse cardiovascular events that was higher in the testosterone group than in the placebo group. However, caution is warranted in interpreting this finding, because of the small numbers of events and because of limitations with respect to the ascertainment of adverse events. Caution is also warranted in extrapolating these find-

Table 5. Changes in Measures of Muscle Performance and Physical Function from Baseline to the End-of-Study Assessment, among Men Receiving Testosterone Therapy.*

Strength and Performance Measures	Testosterone		Placebo		Difference between Treatments			
					Unadjusted		Adjusted for Baseline Mobility	
	no. of men	*mean (95% CI)*	*no. of men*	*mean (95% CI)*	*mean (95% CI)*	*P value*†	*mean (95% CI)*	*P value*‡
Leg-press strength (newtons)	49	156.9 (89.2 to 224.6)	54	27.1 (−28.3 to 82.6)	129.8 (43.9 to 215.6)	0.003	129.4 (43.5 to 215.4)	0.004
Chest-press strength (newtons)	38	34.7 (18.7 to 51.4)	44	0.28 (−13.8 to 14.3)	34.5 (13.2 to 55.8)	0.002	34.5 (13.1 to 56.2)	0.002
Grip strength in dominant hand (kg)	63	1.0 (−0.1 to 2.0)	70	0.7 (−0.3 to 1.7)	0.27 (−1.1 to 1.7)	0.69	0.26 (−1.1 to 1.7)	0.71
50-m walking speed (m/sec)								
Without a load	39	0.074 (−0.004 to 0.153)	43	0.024 (−0.018 to 0.066)	0.050 (−0.035 to 0.135)	0.26	0.048 (−0.037 to 0.133)	0.27
With a load	26	0.139 (0.023 to 0.256)	29	0.065 (0.013 to 0.116)	0.074 (−0.05 to 0.19)	0.24	0.090 (−0.030 to 0.209)	0.14
Stair-climbing power (W)								
Without a load	49	19.5 (7.4 to 31.5)	52	10.7 (−2.9 to 24.3)	8.7 (−9.2 to 26.7)	0.34	8.1 (−9.9 to 26.2)	0.37
With a load	46	39.2 (14.4 to 64.0)	50	9.0 (−8.4 to 26.4)	30.2 (0.3 to 60.1)	0.05	29.7 (0.2 to 59.3)	0.05
Lift-and-lower test§	36	4.4 (2.5 to 6.4)	45	2.6 (0.8 to 4.3)	1.9 (−0.8 to 4.5)	0.16	1.9 (−0.7 to 4.4)	0.15

* The end-of-study assessment was performed either at the end of the 6-month intervention period or at the last visit, if possible, in cases in which the study medication was discontinued before 6 months. Results are reported only for men who were able to perform the relevant tests at baseline. CI denotes confidence interval.

† We calculated the P values in the unadjusted analysis using two-sample Student's t-tests of equal change in the trial groups, allowing unequal variance and using Satterthwaite's approximation to degrees of freedom.

‡ We calculated the P values in the adjusted analysis using multiple linear regression, with adjustment for baseline total score on the Short Physical Performance Battery and self-report of limitations in mobility.

§ The scores on the lift-and-lower test refer to the number of shelves a subject was able to touch with a weighted basket in 1 minute. Higher scores indicate better performance.

ings to other doses and formulations of testosterone or to other populations, particularly young men who have hypogonadism without cardiovascular disease or limitations in mobility.

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APPENDIX

The members of the data and safety monitoring board are as follows: E. Orwoll (chair), A. Newman, K. Schechtman, W. Meikle, and M. Litwin.

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